REMARKS

Applicants respectfully request reconsideration of this application in view of the above Amendment and the following remarks.

Pending in this Application are Claims 1 – 14, 16 – 20, 24, and 29. Claims 21 – 23, 25 – 28, 30, and 31 stand withdrawn as being directed to non-elected species and have also been amended. Claims 15 and 32 – 37 are cancelled.

Applicants have amended pending Claims 1, 4, 6, 8, 10, 13, 14, 16, 18, 19, 24, and 29.

I. Specification

Applicants have amended the specification above to correct the abbreviations for "SEQ ID NO." Applicants have also amended the brief description of figures and the specification between ¶¶0084 – 0085 to insert SEQ ID NO's for those sequences not previously identified.

Applicants hereby submit in conjunction with this response a substitute Sequence Listing and two (2) copies of a substitute compact disc containing the Sequence Listing. The substitute Sequence Listing and the replacement compact discs contain no new matter. The Sequence Listing has been amended to correct the title of SEQ ID NO: 6 to "Sequence for an analog **rat** GHRH sequence." SEQ ID NO: 6 was mistakenly identified as a sequence for an analog **porcine** GHRH sequence in the original version. Support for this correction can be found in Figure 9 and Paragraph 27, which identify the analog rat GHRH sequence. The remainder of the substitute Sequence Listing contains newly added SEQ ID NO's to correspond to those sequences identified in the figures and Paragraphs 21 – 41 and 84 – 85.

II. Rejections Under 35 U.S.C. §112, First Paragraph

Claims 1 – 17, 19, and 20 stand rejected under 35 U.S.C. §112, first paragraph, as being non-enabled. The Examiner asserts that the specification is enabling for a synthetic mammalian expression plasmid comprising a nucleic acid encoding GHRH, but is not enabling for all synthetic mammalian expression plasmids. Applicants respectfully assert that the claims as amended, which pertain to a common promoter and plasmid backbone, do not describe unpredictable subject matter and can be carried out without undue experimentation.

Most importantly, examples pertaining to different expression plasmids can be found in the specification. Starting at Paragraph 6, the specification describes not only growth hormone releasing hormone, but also growth hormone and insulin-like growth factor I, which are molecules with very different molecular weights, biological properties and half-lives. Paragraph 12 cites other articles using this plasmid mediated approach with different genes, providing further examples and evidence that such expression plasmids were already known in the art. In particular, Aihara (1998) described plasmids encoding for interleukin 5 (IL-5); Lesbordes (2002) describes plasmids encoding for cardiotrophin-1 (CT-1). Danko (1994) describes plasmids encoding for luciferase, beta-galactosidase and cloramphenicol acetyl transferase (CAT). Wolff (1992) describes plasmids encoding for CAT and luciferase. All these constructs have different promoters and plasmid backbones. Thus, based on the information provided in the specification itself, examples of molecules belonging to many classes, with different properties, have all been used in the plasmid context.

Applicants respectfully assert that most of the literature cited by the Examiner is outdated, considering the filing date of the application is July 2003 and the art of gene supplementation is rapidly changing and improving. The most recent reference cited by the Examiner was published in 2001. In view of this outdated art, it is not appropriate to make the assertion that gene supplementation was unpredictable using the disclosed technology and procedures as of 2003.

Furthermore, Applicants assert that the literature is not relevant to the elected claims. First, the elected claims do not pertain to methods of gene delivery, but rather to a synthetic mammalian expression plasmid that was optimized for length and strength of expression. Discussions in the literature of gene delivery methods and difficulties encountered in connection with these methods are simply not relevant to claims on an expression plasmid. The references do suggest that the delivery method for plasmids has been a problem, because simple injection results in low uptake, irrespective of the type of transgene or type of plasmid. This is clearly irrelevant to the claims. Second, the references deal with viral vectors, while the claims pertain to expression DNA plasmids. Third, the references suggest that commercial plasmids have been immunogenic in a multitude of situations due to bacterial sequences present in their backbones, resulting in short term transgene expression. This is precisely the problem that the current claims

solve, as they use optimized, synthetic sequences in the claimed expression plasmid. Finally, the Examiner has expressed the argument that the claims are not enabled for different gene sequences within a single vector, while the references complain of difficulties encountered with different vectors. Nowhere in the cited references is it suggested that gene supplementation may be unpredictable using different genes in association with a common promoter and plasmid backbone.

Specifically, in the Verma (1997) publication, the possible advantages and pitfalls of the different types of gene therapy vectors are described. Verma indicates that at the time of the publication of the article no "perfect" gene delivery system was found. Nevertheless, nowhere in the article is it suggested that using the same plasmid backbone with the same promoter, but with different transgenes, would result in an "unpredictable" expression pattern. On the contrary, Verma clearly states: "The first comprises the non-viral vectors.... Most of these approaches suffer from poor efficacy of delivery and transient expression **of the gene** (*i.e* any gene)". In the instant claims, gene delivery is not relevant. A more accurate explanation of the teachings of Verma is that it states that there is NO difference between one transgene and another with regard to the pitfalls of a particular vector.

The Examiner also cites Marshall (1995). This citation raises the same issue as Verma. Again, the author states clearly: "Gene therapists still encounter difficulties in **transferring genes** (emphasis added – *i.e.* any gene) to adequate numbers of target cells and getting them expressed." Please notice that again, in the current claims the delivery method is not at issue.

The Orkin (1995) citation is also similar to the two above. To cite from this document, please refer to point 3: "Major difficulties at the basic level include shortcomings of all current gene therapy vectors and an inadequate understanding of the biological interactions with the host." Again, the authors refer to the vectors, and NOT to genes that are encoded by the vectors, and do not differentiate the utility of a certain vector based on the transgene. Furthermore, the current claims pertain to plasmid vectors that are better characterized, safer and that include only desired elements (properly designed and synthesized), rather than bits and pieces from commercially available or laboratory clones and sub-cloned gene therapy vectors, eliminating

elements that were either not well characterized, or that were known in the literature to impact negatively the plasmid persistence or expression levels.

In Eck (1996), the author underlines the vector uptake and degradation, the duration of expression of a transferred gene (which is actually function of plasmid backbone design and promoter activity), and adverse consequences of heterologous gene expression. Eck **does not suggest** that using the same plasmid backbone, with the same promoter, one would get "unpredictable results".

The Ross (1996) publication also pertains to delivery methods. The current claims describe new, innovative plasmids, and do not focus on a delivery method. This article also compares the different types of gene therapy vectors, and points out (see for instance page 1783, second column): "The remaining...plasmid DNA (1.9%)... Although these systems appear INHERENTLY more attractive due to their simplicity, usual inability to elicit adverse immune responses to the vectors, and ease of production, their efficiency in gene delivery appears to be lagging significantly behind the viral delivery systems." This patent application is directly related to the creation of simpler, cleaner, better characterized, plasmids containing optimized elements.

As pointed out by the Examiner, Rubanyi (2001) describes the pitfalls of the different delivery vectors, as well as their cellular targeting and trafficking, their impact on the immune system, and their more or less usefulness for the different types of applications. The Examiner takes out of context a small citation from Rubanyi on page 131, but does not cite page 132, where the author describes those hurdles. None of the difficulties have anything to do with the custom design of plasmids. The author describes the match of therapeutic protein to the disease, the gene delivery vector to match the disease, route of vector delivery, GMP production, etc. The author even states later on the same page that therapeutic benefits can be achieved by transfection/transduction of some (but not all) target cells because these cells (for instance, in the case described by the author, cardiac myocytes) will serve as "factories" for production of the secreted growth factor protein." Again, the author does not imply in any way that using an optimized plasmid for producing hormones, enzymes, or proteins and any other molecules that

are secreted into the blood stream would be "unpredictable". The problem solved by the claims is the choice of vector.

In Schwaab (2001), the author describes gene therapeutic approaches for hemophilia using retroviruses, adenoviruses or adeno-associated viruses, and not plasmids. The current claims focus on the pitfalls of these vectors, and on the antibodies that are produced against factor VIII or factor IX, if the subjects never had a normal factor VIII or IX produced. This is a very old problem in medicine, and it is not linked to gene therapy. It has been described for many conditions, including hemophilia, as a person of skill in the art would know. A vast literature pre-exists the gene therapy era, when recombinant proteins were used, including purified factor VIII or IX. When subjects were affected by genetic diseases and never produced the normal protein, they were given the recombinant protein. In many circumstances these patients developed antibodies against the normal recombinant protein, but in a majority of cases these antibodies were not neutralizing, and the therapy was partially successful. It is in the common medical practice to screen the patients for this unfortunate possibility irrespective of the molecule involved, not only for gene therapy approaches, but for the recombinant protein therapies. This is not "undue" experimentation, but common sense to ordinary practitioners.

Rissanen (2001) talks about the different recombinant proteins and gene therapy vectors used for the treatment of the ischemic lower limb. As a matter of fact, the author (see page 656, second column, second paragraph) even admits that from all the vectors, plasmid DNA (naked DNA) "is still often used in skeletal muscle. Transfection efficacy of naked DNA in skeletal muscle is usually low but can be increased using techniques generating muscle damage and regeneration." Furthermore, the current claims pertain to new, better designed plasmids that avoid some of the problems of older plasmid versions, *i.e.* an inflammatory response due to the presence of CpG islands in the plasmid backbone. Furthermore, the Examiner cites that "improvement is needed in gene transfer efficiency..." The claims relate to better plasmids, not to a delivery method.

The issue in Emanueli (2001) is similar to Rissanen. The article describes that different types of viral vectors, in particular adenoviruses, adeno-associated viruses and lentiviruses, have been used with variable results. A bright spot in the constellation of therapies described can be

found on page 954, first column, 4th paragraph in its entirety. It states: "Therapeutic angiogenesis has been successfully extended from bench to bedside. Isner was the first to demonstrate that arterial gene transfer of NAKED DNA encoding for VEGF165 (phVEGF165) at dosages from 100-2000 μg improves limb perfusion and relives rest pain in patients with critical peripheral ischemia." Emanueli has little to do with the current claims, and the portions cited by the Examiner are out of context considering the actual teachings of the entire reference.

The Examiner cites from MacColl (1999) to describe the problems that existed related to the use of plasmids. In particular, "plasmid based vectors have also been shown to be immunogenic, as these contain immunostimulatory DNA sequences (ISS) which stimulate both macrophages and T lymphocyte based immune responses..." In the current application, a methodology and novel plasmids are described that present a comprehensive and innovative solution to exactly this problem. The plasmids described in the application and claims are synthetic and include only desired elements.

Thus, the references cited by the Examiner do not indicate that the claimed subject matter is non-enabled because these references pertain to entirely different problems and unpredictabilities. The claims, as amended, are directed to expression plasmids that are non-viral, synthetic, contain a common promoter and plasmid backbone, and are optimized to avoid immunogenic effects. The claimed subject matter avoids the problems of the prior art and is clearly enabled.

III. Rejections Under 35 U.S.C. §112, Second Paragraph

Claims 1 – 20 and 24 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite.

The Examiner has rejected Claims 1 – 20 for being indefinite based on the phrase "codon-optimized-eukaryotic therapeutic gene sequence." The Examiner asserts that this phrase is indefinite because the optimization varies with regard to the host organism and the claims do not specifically describe which host organism is contemplated. Applicants have amended Claim 1 to specify that the synthetic mammalian expression plasmid is for plasmid mediated gene supplementation in a species and that the codon-optimized-eukaryotic therapeutic gene sequence

has at least one codon modification that is specific to the species. Applicants respectfully assert that a person of ordinary skill in the art when reading the specification will understand that optimization certainly depends on the choice of gene sequence and the choice of species and does not require any further guidance in the claim language.

Claim 1 has been amended to more clearly describe the species-specific nature of the optimization. Claim 1 requires that the synthetic mammalian expression plasmid be used for plasmid mediated gene supplementation in a particular species. Claim 1 further requires that the codon-optimized-eukaryotic therapeutic gene sequence contain at least one modification that is optimized for that species. Thus, even though the specific species is not listed, it is clear that the optimization is particular to the species being targeted for the plasmid mediated gene supplementation. A person of skill in the art would obviously know which species upon which he or she is intending to use the plasmid mediated gene supplementation. Thus, that person of skill in the art would clearly be able to pick out the optimized codons for that species. The claims do not need to list the particular species, as that limitation is unnecessary in view of the guidance given in the specification and the capabilities of those of skill in the art.

The specification provides plenty of examples of species-specific optimization, including mouse, rat, bovine, ovine, etc. There is no possible doubt that a person of skill in the art knows that when dealing with a cow, the "codon optimization" is for bovine. That person of skill in the art could very easily locate the appropriate optimized codons for that species. Figure 27 of the current application shows publicly available databases references for optimized codons. Also, the definition of the term "optimized codon" is clearly given in the specification at paragraph [0048]: "The term 'optimized codon' as used herein refers to a codon that has a match codon frequency in target and host organisms, but does not alter the amino acid sequence of the original translated protein. The optimized codons of this invention were determined using Aptagen's Gene Forge® codon optimization and custom gene synthesis platform (Aptagen, Inc., 2190 Fox Mill Rd. Suite 300, Herndon, VA 20171). Other publicly available databases for optimized codons are available and will work equally as well." These databases are indicated in Figure 27.

Applicants respectfully assert that the Federal Circuit's *Orthokinetics* case is precisely on point with regard to this claim language. The *Orthokinetics* case dealt with a patent claiming a

collapsible pediatric wheelchair sized to fit between the doorframe and the seat of an automobile, but the claims did not pertain to any specific automobile. *See Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 1 U.S.P.Q.2d 1081, 1088 (Fed. Cir. 1986). The district court found this limitation to be indefinite because an accused infringer would have no idea of knowing whether the claim was infringed without testing the chair on every known model of automobile. *See id.* The Federal Circuit soundly rejected this reasoning, indicating that **the lower court had incorrectly used and applied the statutory language pertaining to indefiniteness and had improperly required that the claim "describe" the invention, which is actually the role of the written description**. *See id.* Because automobiles are necessarily of different sizes, the phrase "so dimensioned" was as accurate as possible. *See id.* The statutory requirements of §112, second paragraph, were satisfied so long as those of ordinary skill in the art knew that the appropriate dimensions could easily be obtained. *See id.*

Similar to the claims in *Orthokinetics*, the current claims do not have to spell out each possible host organism to be definite. A person of ordinary skill in the art will be able to identify the desired species and locate the optimized codons for that species without difficulty. It is not necessary for the claims to describe the invention – that is the job of the written description. In this case, the written description provides ample guidance as to how to locate optimized codons for a desired species. Thus, in view of these arguments and the amendment to Claim 1, the phrase "codon-optimized-eukaryotic therapeutic gene sequence" is definite.

The Examiner has also asserted that the phrase "selectable marker gene promoter" is indefinite because it does not require that the promoter drive expression of the selectable marker gene in the construct. Applicants have amended Claim 1 to list "selectable marker gene sequence," followed later in the claim by "promoter for the selectable marker gene sequence." Applicants respectfully assert that this amendment clarifies the claim language and is sufficiently definite.

Claims 15, 16, 18, and 24 have also been amended to clarify that the gene sequence is a codon-optimized-eukaryotic therapeutic gene sequence. Thus, Applicants respectfully assert that this claim terminology has antecedent basis in Claim 1.

Due to these amendments and remarks, Applicants respectfully assert that Claims 1 – 20 and 24 satisfy the requirements of 35 U.S.C. §112, second paragraph.

IV. Claim Construction

As already discussed above, Applicants do not agree with the Examiner's interpretation of the claim limitation "codon-optimized." Applicants have amended Claim 1 to provide that the synthetic mammalian expression plasmid is for plasmid mediated gene supplementation in a species and the codon-optimized-eukaryotic therapeutic gene sequence contains codon modification specific to that species. Applicants respectfully assert that this limitation is definite even without a specific identification of a host organism in the claims. A person of skill in the art would be able to choose the species being targeted and would then be fully capable of selecting the optimized codons for that species.

V. Rejections Under 35 U.S.C. §102

A. Draghia-Akli et al. (1997)

Claims 1, 2, 5, 7 – 9, 11, and 14 – 20 stand rejected under 35 U.S.C. §102(b) as being anticipated by Draghia-Akli et al. (1997). The Examiner asserts that this reference discloses a synthetic mammalian expression plasmid with a codon-optimized-eukaryotic therapeutic gene sequence having the broadest interpretation thereof. Applicants respectfully assert that the claims as amended require a species specific codon-optimized eukaryotic therapeutic gene sequence that is not disclosed by Draghia-Akli (1997).

As already discussed, Applicants have amended Claim 1 to provide that the synthetic mammalian expression plasmid is for plasmid mediated gene supplementation in a species and the codon-optimized-eukaryotic therapeutic gene sequence contains codon modification specific to that species. This claim terminology is not indefinite and does not include any eukaryotic therapeutic gene sequence because the gene sequence must be optimized for the species to which the synthetic mammalian expression plasmid is directed.

Draghia-Akli (1997) and the plasmid map for pBS describe **unoptimized, large plasmids** that include a multitude of CpG islands and unnecessary bacterial sequences; for example, the plasmid described in Draghia-Akli is 3,534 bp while the new optimized plasmids described in the current application are approximately 2,739 bp, or approximately 800 bp LESS than the constructs described in Draghia-Akli. Nowhere in Draghia-Akli (1997) is it disclosed that the plasmid should be optimized with codons containing modifications specific to the species for which the plasmid is intended.

The Examiner asserts that the original claims were ambiguous as to "what constitutes a codon optimized sequence and the fact that essentially all codons can be construed as optimized in the absence of a clearly identified reference organism, any docing sequence can be considered to comprise one or more optimized codons." See Office Action, page 16. Applicants respectfully assert that the claims have been amended to be species-specific. Claim 1 requires that the synthetic mammalian expression plasmid be used for plasmid mediated gene supplementation in a particular species. Claim 1 further requires that the codon-optimized-eukaryotic therapeutic gene sequence contain at least one modification that is optimized for that species. Thus, even though the specific species is not listed, it is clear that the optimization is particular to the species being targeted for the plasmid mediated gene supplementation. This concept is not discussed at any point in Draghia-Akli (1997).

Thus, in view of the amendment to Claim 1 and the comments above, Claims 1, 2, 5, 7 – 9, 11, and 14 – 20 are not anticipated by Draghia-Akli (1997).

B. U.S. Patent No. 6,423,693

Claims 1, 2, 5, 7 – 9, 11, and 14 – 20 stand rejected under 35 U.S.C. §102(e) as being anticipated by U.S. Patent No. 6,423,693 to Schwartz et al. ("Schwartz '693"). The Examiner asserts that Schwartz '693 describes vectors similar to those in Draghia-Akli and similarly anticipates the claims.

Applicants respectfully assert that Claim 1 has been amended to provide that the synthetic mammalian expression plasmid is intended for plasmid mediated gene supplementation

in a particular species and that the codon-optimized-eukaryotic therapeutic gene sequence in the plasmid has at least one codon modification specific to the species. In other words, the optimized codons are specific to the species for which the plasmid is intended to be administered. As with Draghia-Akli (1997), Schwartz '693 does not describe this type of species-specific codon optimization, and the plasmids contain unnecessary sequences that account for approximately 800 bp. Thus, Schwarts '693 does not anticipate the claims as amended.

The Examiner notes that Schwartz '693 does teach embodiments in which the GHRH sequence is optimized. See Office Action, page 18. However, an analysis of this section of Schwartz '693 reveals that it does not describe the optimization of codons in a species-specific manner, depending on the species to which the plasmid is to be administered.

Thus, in view of the amendment to Claim 1 and the comments above, Claims 1, 2, 5, 7 – 9, 11, and 14 – 20 are not anticipated by Schwartz '693.

C. U.S. Patent No. 6,551,996

Claims 1 – 9 and 11 – 20 stand rejected under 35 U.S.C. §102(e) as being anticipated by U.S. Patent No. 6,551,996 to Schwartz et al. ("Schwartz '996"). The Examiner asserts that Schwartz '996 describes an optimized plasmid backbone that corresponds to the plasmid of the current claims.

Again, Applicants respectfully assert that Claim 1 has been amended to provide that the synthetic mammalian expression plasmid is intended for plasmid mediated gene supplementation in a particular species and that the codon-optimized-eukaryotic therapeutic gene sequence in the plasmid has at least one codon modification specific to the species. In other words, the optimized codons are specific to the species for which the plasmid is intended to be administered. Schwartz '996 does not describe this kind of codon optimization.

It is inevitable that plasmids will have some common structural features – they are plasmids. However, the currently claimed plasmids contain elements that have been optimized

by design and synthesized to be species-specific. Thus, in view of the amendment to Claim 1 and the comments above, Claims 1 – 9 and11 – 20 are not anticipated by Schwartz '996.

D. International Patent Application Publication No. WO 01/06988

Claims 1 – 9 and 11 – 20 stand rejected under 35 U.S.C. §102(b) as being anticipated by International Patent Application Publication No. WO 01/06988 to Schwartz et al. ("Schwartz '988"). The Examiner asserts that the disclosure of Schwartz '988 is identical to that of Schwartz '996 and therefore the claims are similarly anticipated.

Applicants respectfully assert that the claims are not anticipated by Schwartz '988 for the same reasons they are not anticipated by Schwartz '996. Neither Schwartz '988 nor Schwartz '996 disclose synthetic mammalian expression plasmids that contain codons in a therapeutic gene sequence that have been optimized for the particular species to which the plasmids are to be administered.

Thus, in view of the amendment to Claim 1 and the comments above, Claims 1 – 9 and11 – 20 are not anticipated by Schwartz '988.

VI. Nonstatutory Double Patenting

Claims 1, 2, 5, 7 – 9, 11, and 14 – 20 stand provisionally rejected as being obvious and not patentably distinct in view of U.S. Patent No. 6,423,693 to Schwartz et al. ("Schwartz '693"). The Examiner asserts that Schwartz '693 describes vectors that include the same elements as those in the current claims and therefore is not patentably distinct from the claims.

As discussed with regard to Schwartz' 693 above, the current claims have been amended to provide that the synthetic mammalian expression plasmid is intended for plasmid mediated gene supplementation in a particular species and that the codon-optimized-eukaryotic therapeutic gene sequence in the plasmid has at least one codon modification specific to the species. In other words, the optimized codons are specific to the species for which the plasmid is intended to be administered. Schwartz '693 neither discloses, teaches, nor suggests such species-specific optimization; the plasmids in '693 contain unnecessary elements that account for almost 800 bp.

Thus, the claims of the current application are patentably distinct from the teachings of Schwartz '693. Applicants respectfully request that this provisional rejection for double patenting be withdrawn.

VII. Conclusion

Applicant has addressed each of the Examiner's comments in the Office Action dated August 24, 2006. Applicant respectfully submits that, in light of the foregoing comments, Claims 1 – 14, 16 – 20, 24, and 29 are in condition for allowance. A Notice of Allowance is therefore requested.

If the Examiner has any other matters which pertain to this Application, the Examiner is encouraged to contact the undersigned to resolve these matters by Examiner's Amendment where possible.

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